FIG. 1

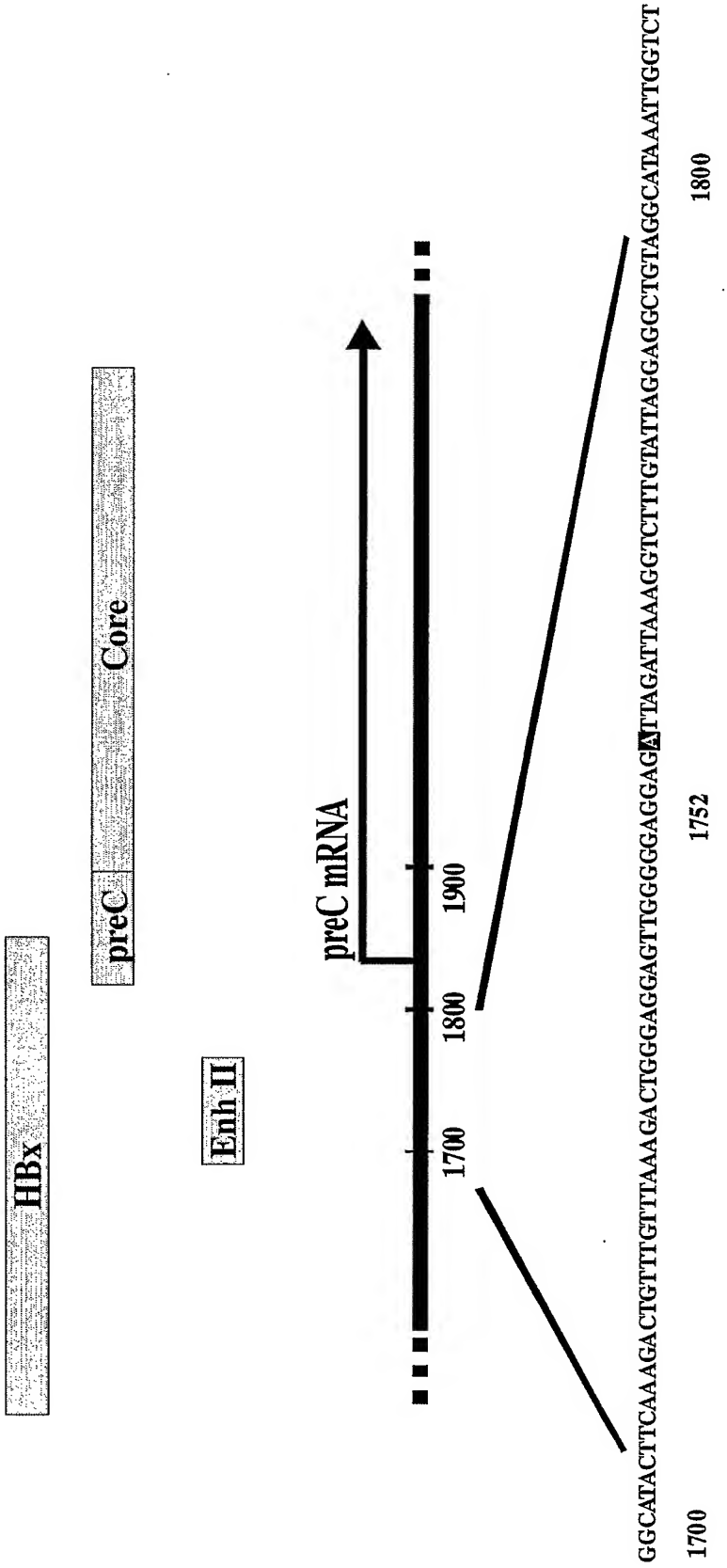

HBx
preC
Core
Enh II
preC mRNA
1700
1800
1900
1700
1752
1800
GGCATACTTCAAAGACTGTTTGTTTAAAGACTGGGAGGAGTTGGGGGAGGAGATTAGATTAAAGGTCTTTGTATTAGGAGGCTGTAGGCATAAATTGGTCT

FIG. 2

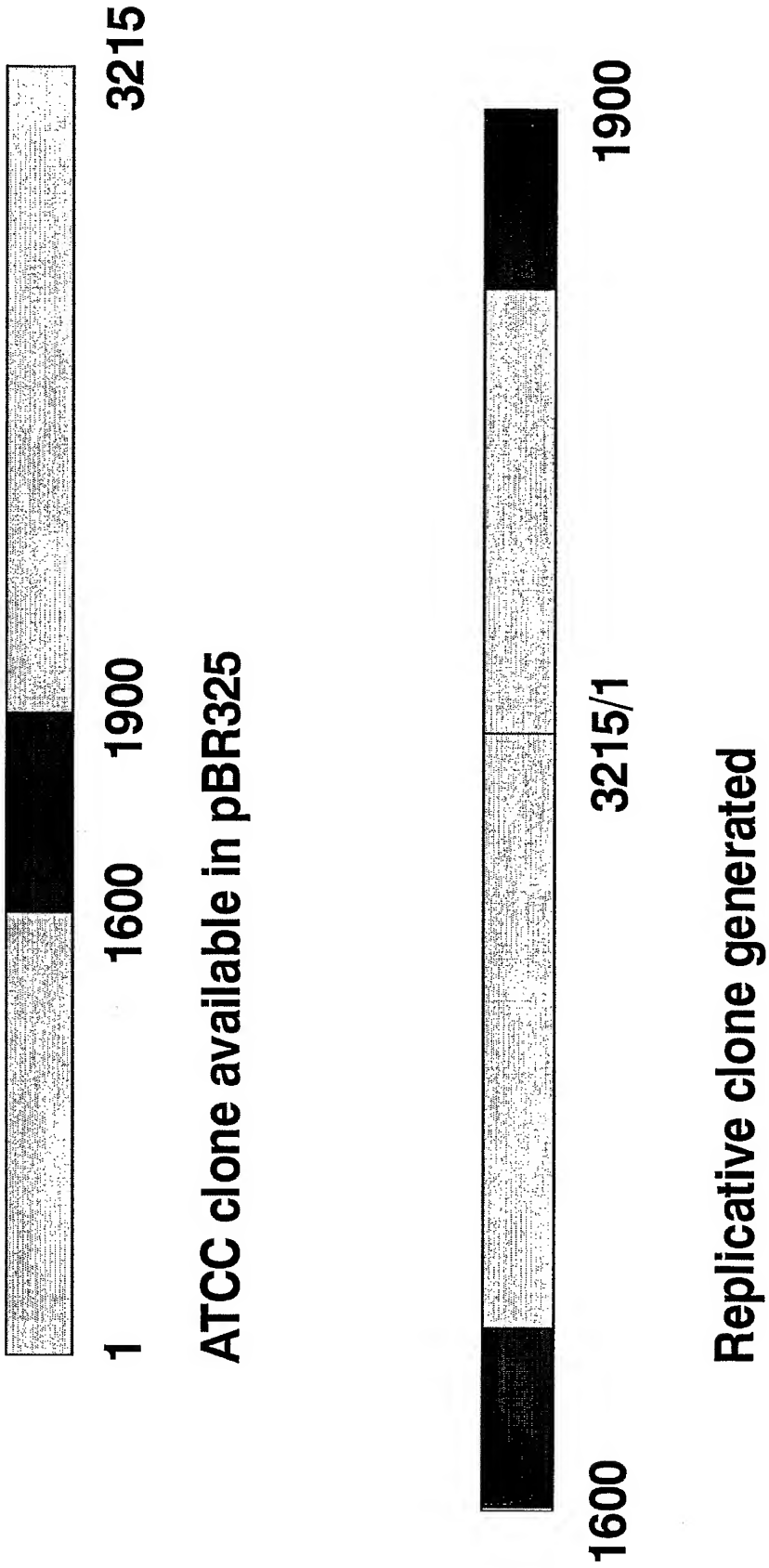

1
1600
1900
3215
ATCC clone available in pBR325
1600
3215/1
1900
Replicative clone generated

FIG. 3

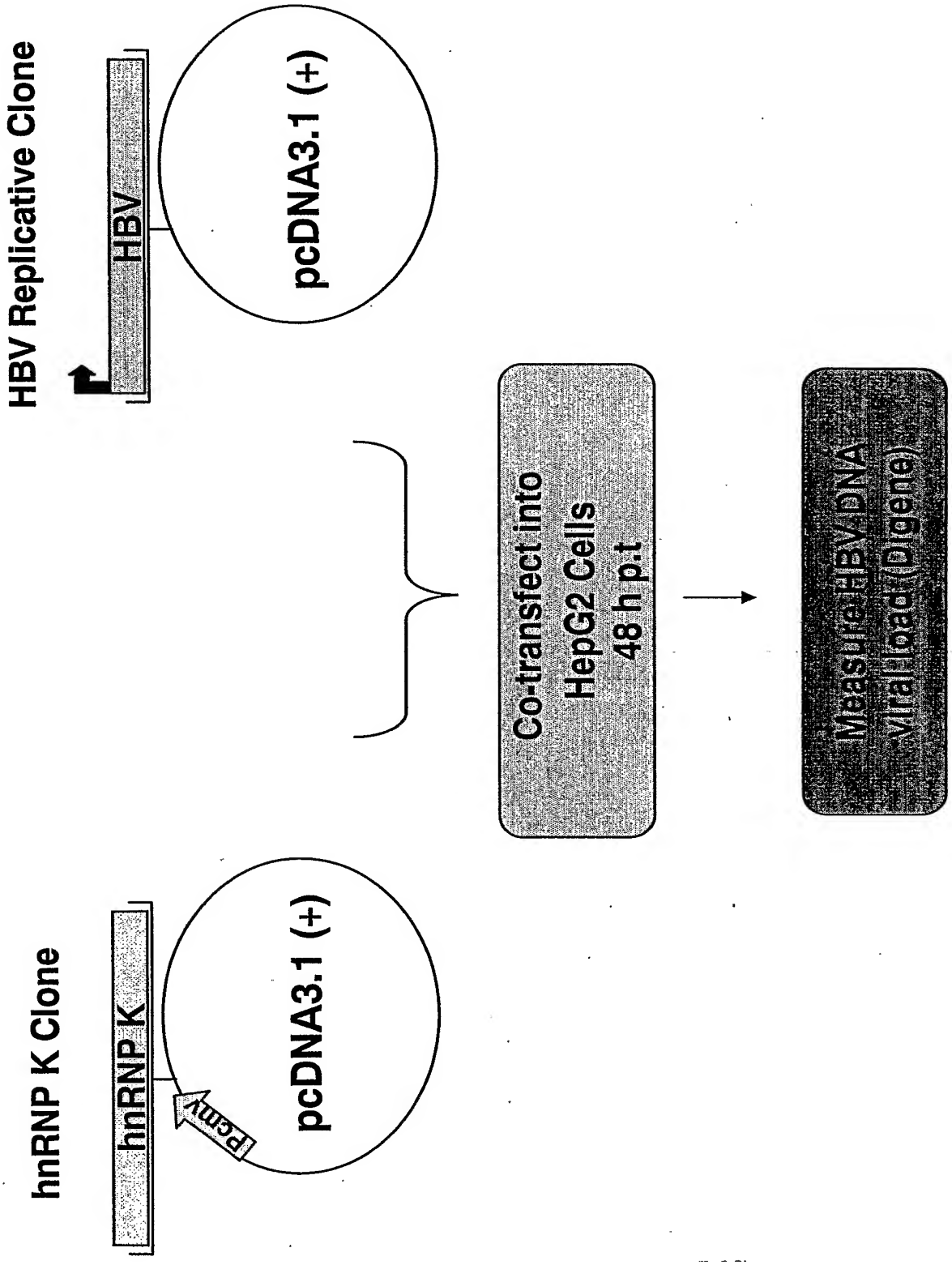

HBV Replicative Clone
HBV
pcDNA3.1 (+)
hnRNP K Clone
hnRNP K
PCMV
pcDNA3.1 (+)
Co-transfect into
HepG2 Cells
48 h p.t
Measure HBV DNA
viral load (Digene)

FIG. 4

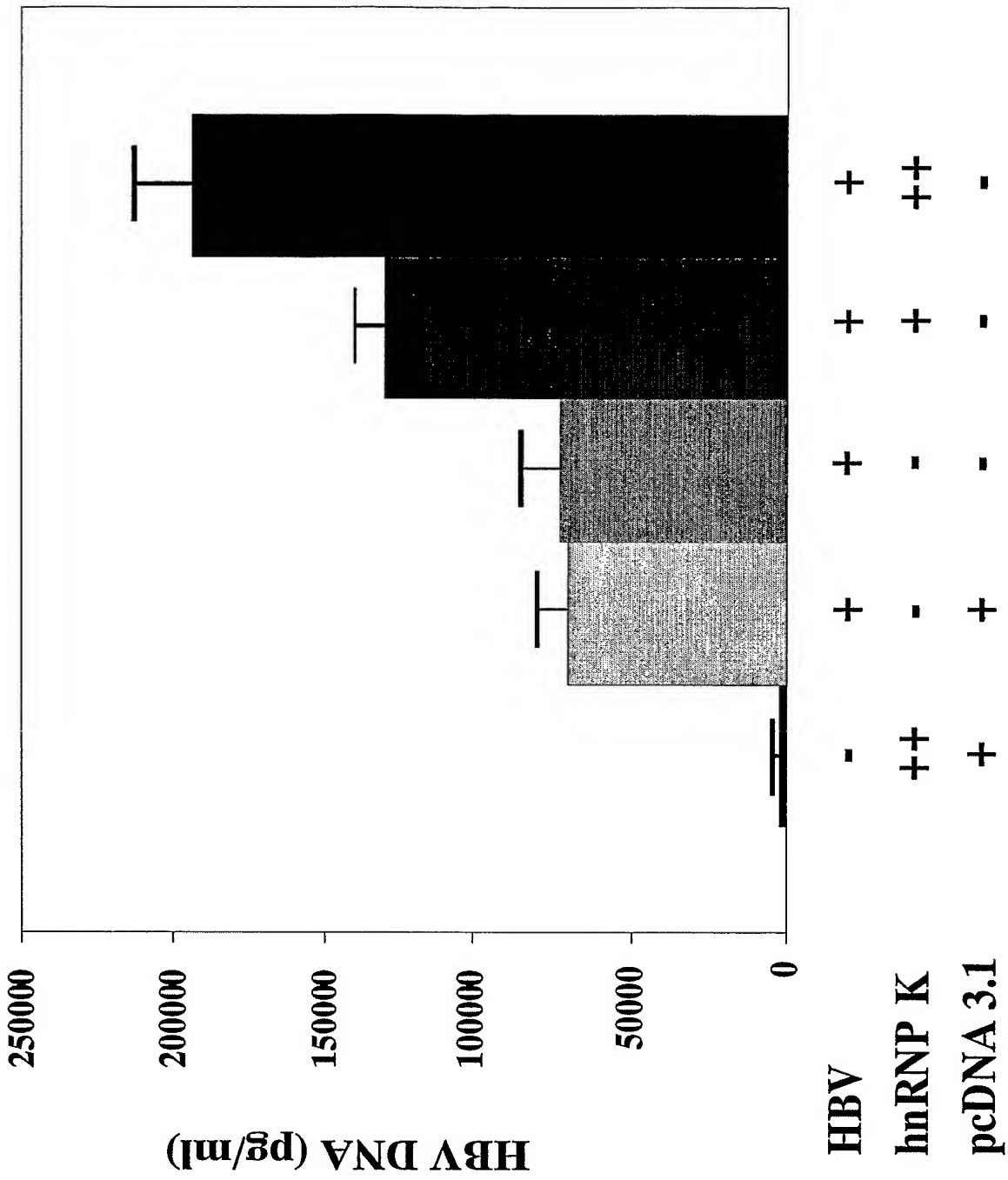

HBV DNA (pg/ml)
250000
200000
150000
100000
50000
0
HBV
hnRNP K
pcDNA 3.1
+ + + + -
+ + - + -
+ - - + -
+ - + + -
- ++ + -

FIG. 5

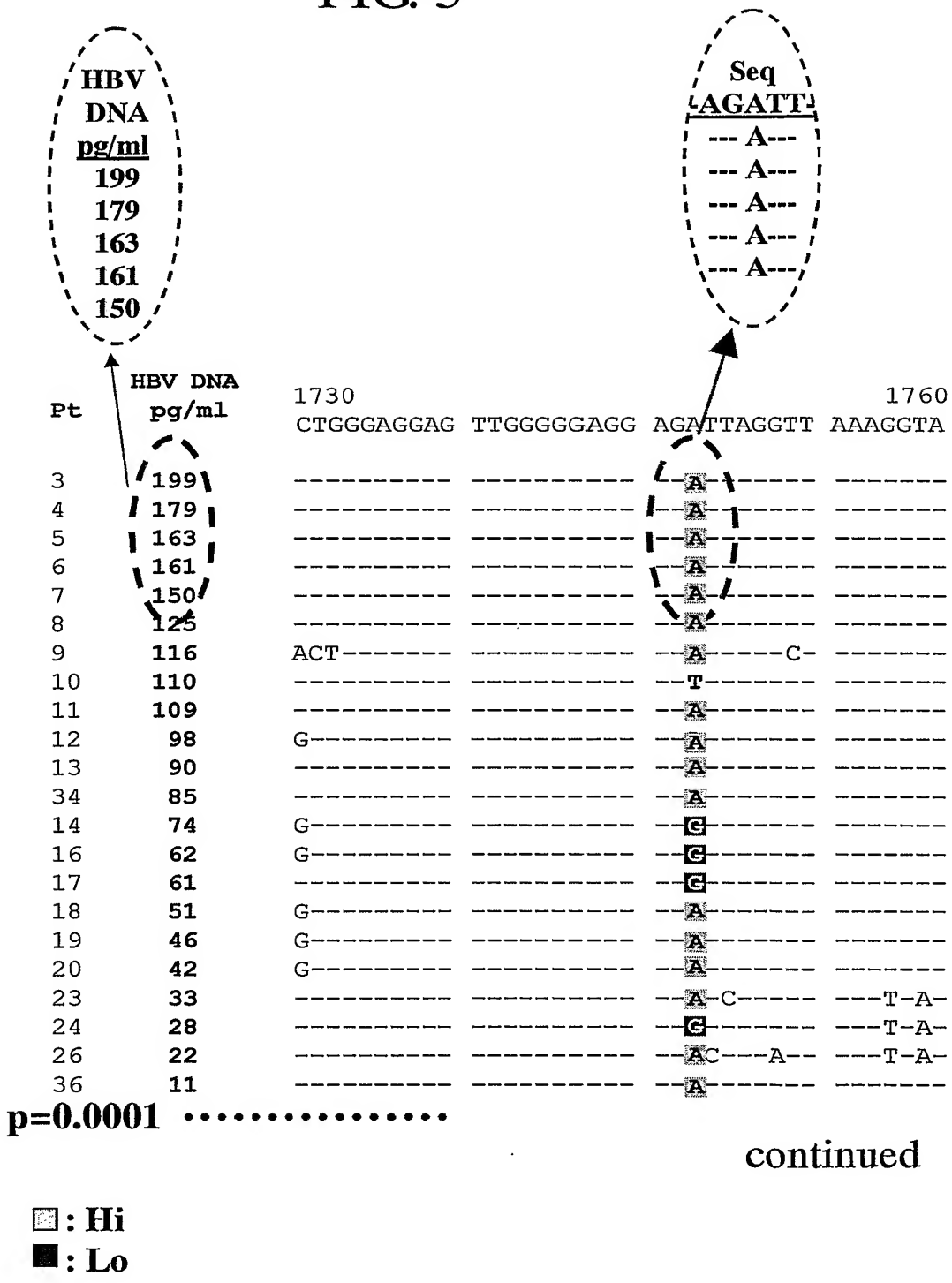

HBV DNA pg/ml
199
179
163
161
150
Seq AGATT
--- A---
--- A---
--- A---
--- A---
--- A---
Pt
HBV DNA pg/ml
1730
1760
CTGGGAGGAG TTGGGGGAGG AGATTAGGTT AAAGGTA
3 199
4 179
5 163
6 161
7 150
8 125
9 116
10 110
11 109
12 98
13 90
34 85
14 74
16 62
17 61
18 51
19 46
20 42
23 33
24 28
26 22
36 11
p=0.0001
continued
: Hi
: Lo

FIG. 5

- continuation -

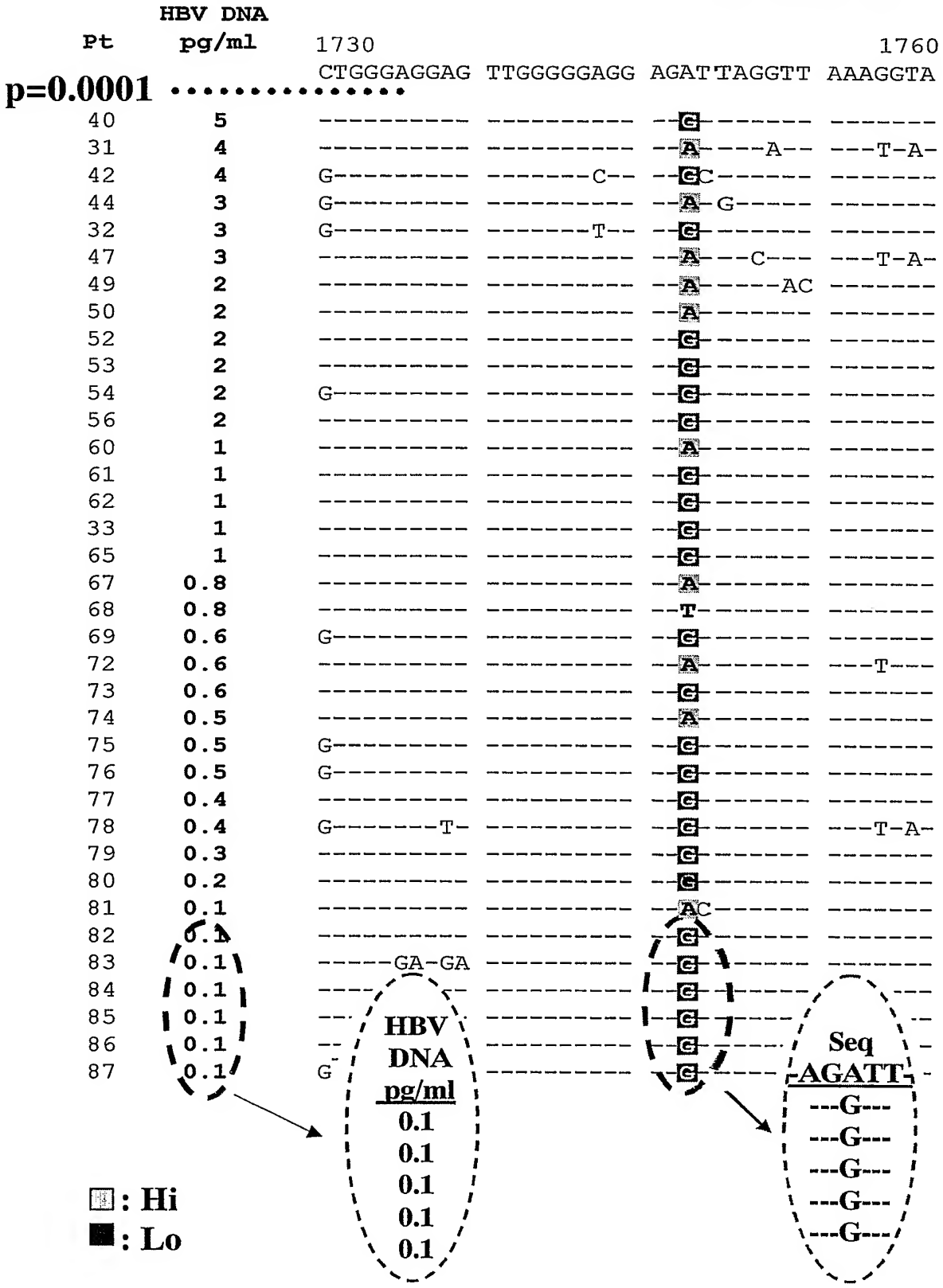


FIG. 6

1687

GAC CGACCTTGAG GCATACTTCA AAGACTGTTT GTTTAAAGAC TGGGAGGAGT

1741

TGGGGGAGGA GATTAGGTTA AAGGTCTTTG TACTAGGAGG CTGTAGGCAT AAATTGGTCT

1801

GTTCA

FIG. 7

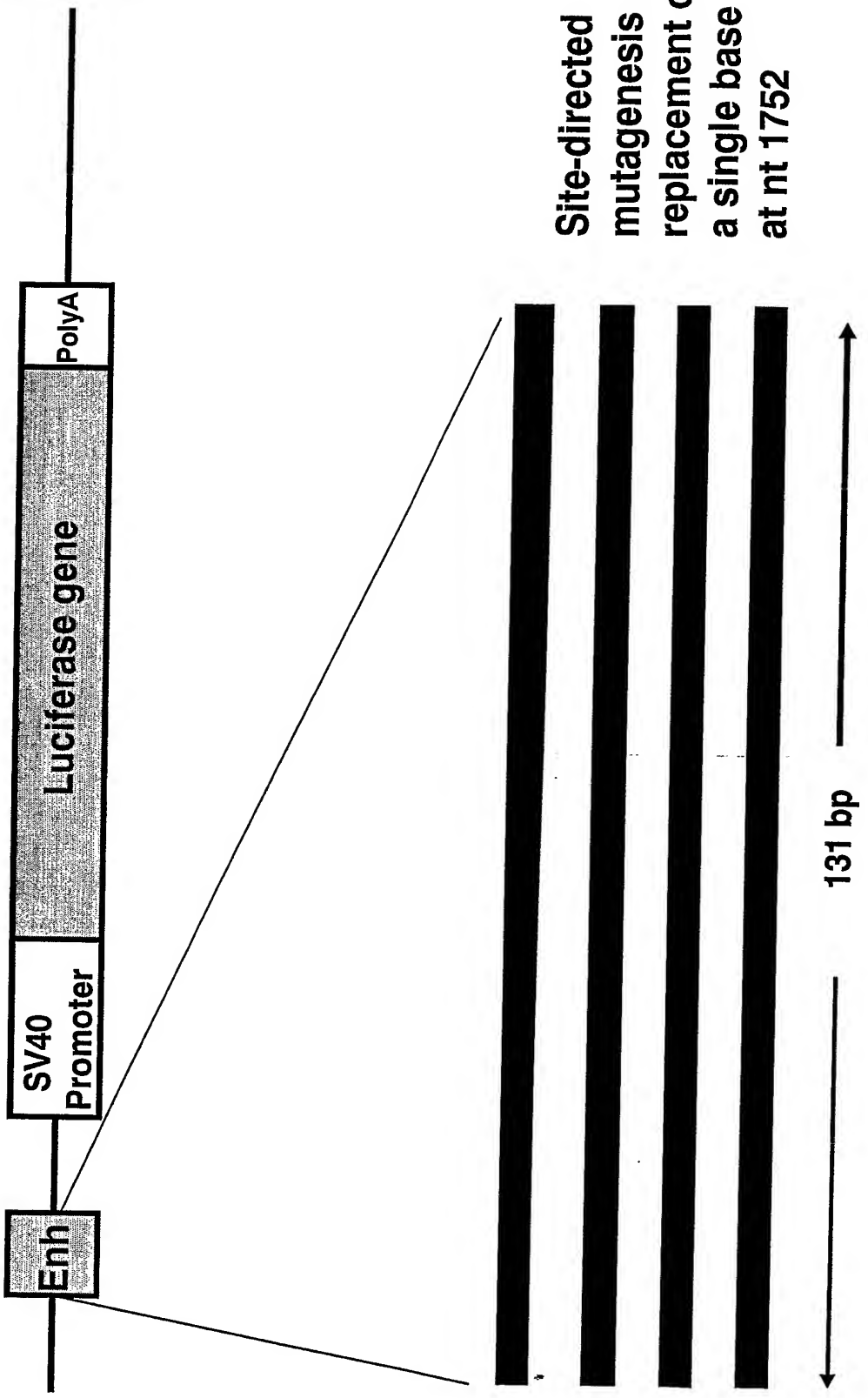

Enh
SV40 Promoter
Luciferase gene
PolyA
Site-directed mutagenesis replacement of a single base at nt 1752
131 bp

FIG. 8

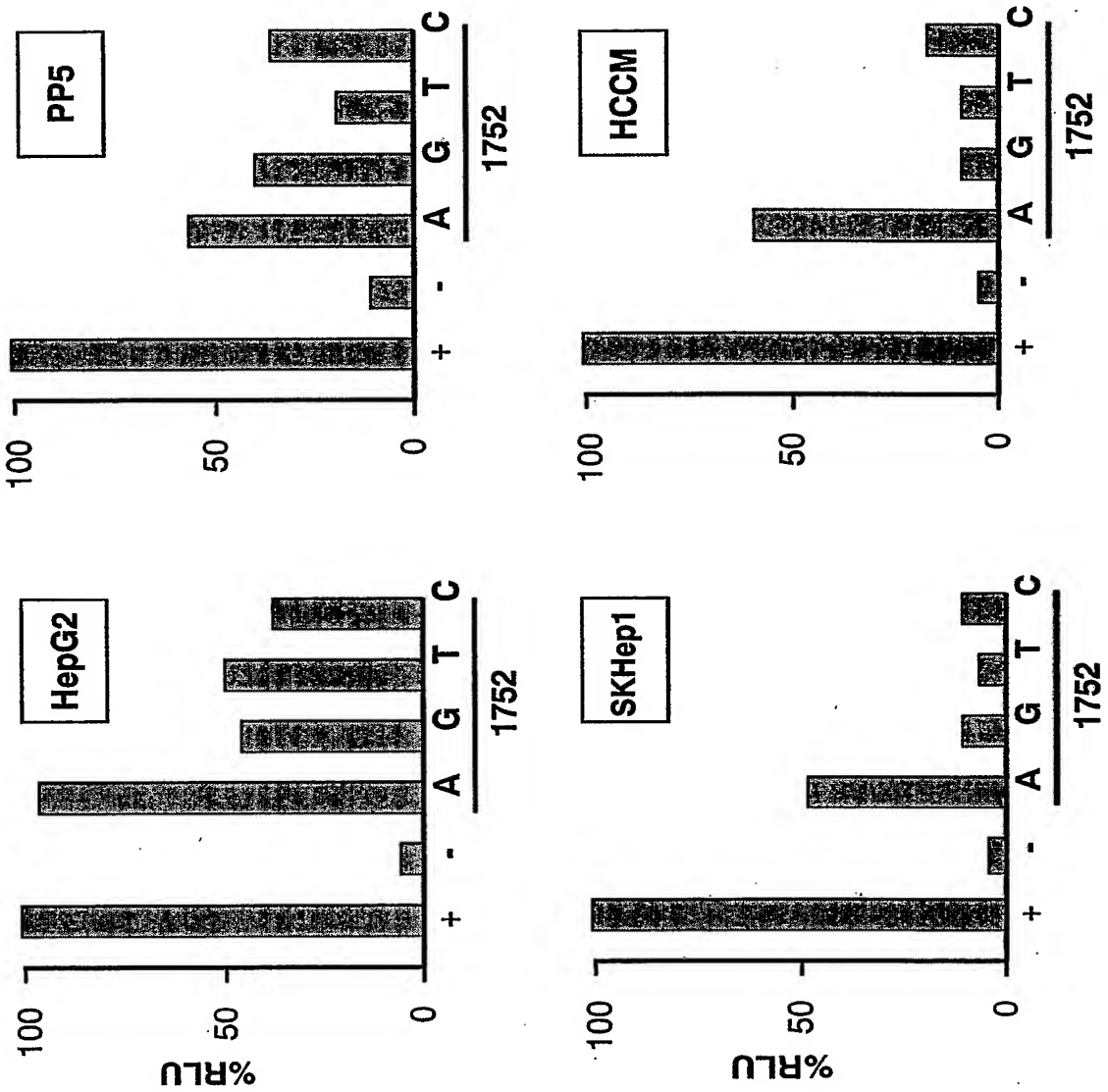


FIG. 9

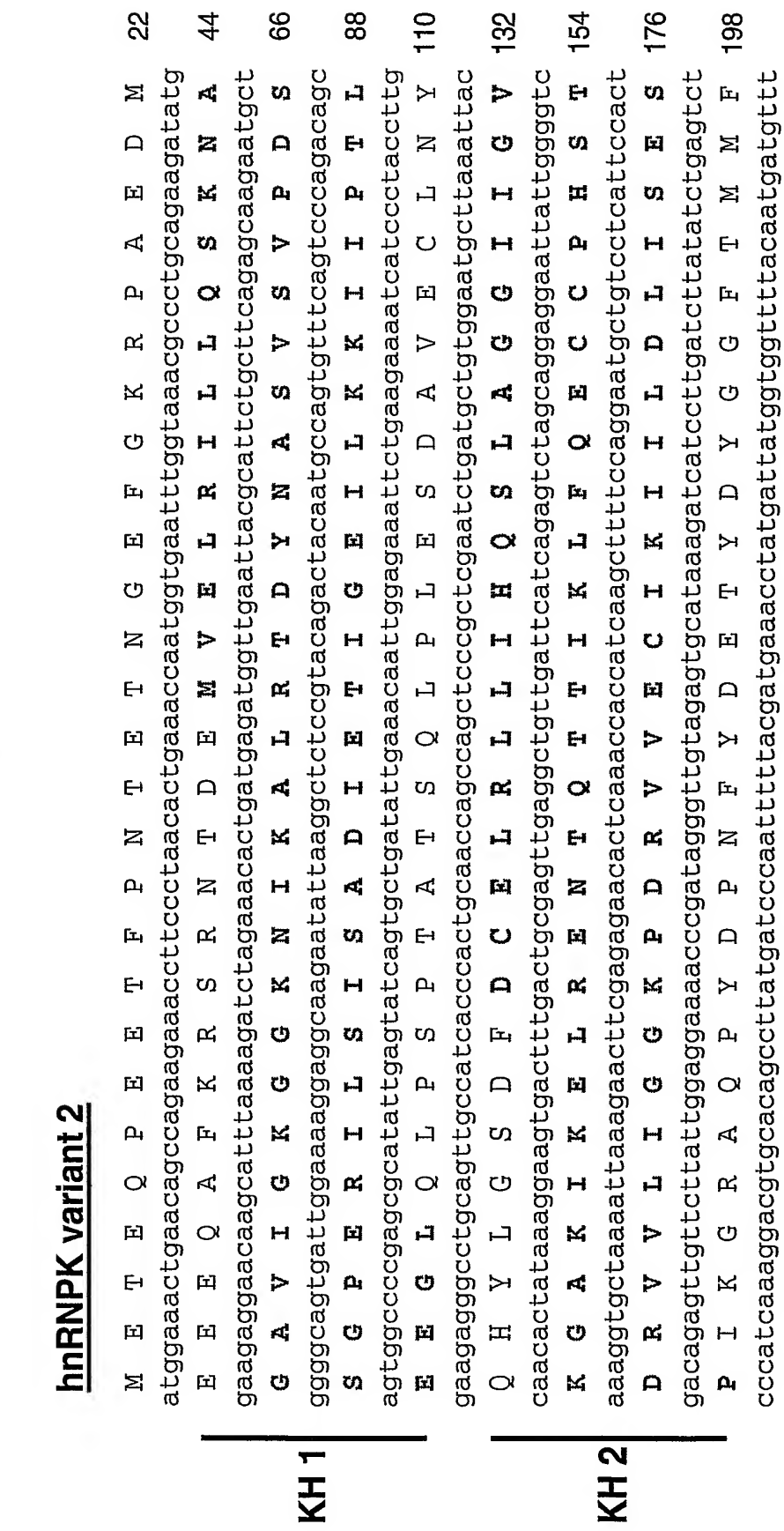

hnRNPK variant 2
KH 1
KH 2
M E T E Q P E E T F P N T E T N G E F G K R P A E D M 22
atggaaactgaacagccagaagaaaccttccctaacactgaaaccaatggtgaatttggtaaacgccctgcagaagatatg
E E E Q A F K R S R N T D E M V E L R I L L Q S K N A 44
gaagaggaacaagcatttaaaagatctagaaacactgatgagatggttgaattacgcattctgcttcagagcaagaatgct
G A V I G K G G K N I K A L R T D Y N A S V S V P D S 66
gggcagtgattggaaaaggaggcaagaatattaaggctctccgtacagactacaatgccagtgtttcagtcccagacagc
S G P E R I L S I S A D I E T I G E I L K K I I P T L 88
agtggccccgagcgcatattgagtatcagtgctgatattgaaacaattggagaaattctgaagaaatcatccctacctttg
E E G L Q L P S P T A T S Q L P L E S D A V E C L N Y 110
gaagagggcctgcagttgccatcacccactgcaaccagctcccgctcgaatctgatgctgtggaatgcttaaattac
Q H Y L G S D F D C E L R L L I H Q S L A G G I I G V 132
caacactataaaggaagtgacttttgactgcgagttgaggctgttgattcatcagaggaggaattattgggggtc
K G A K I K E L R E N T Q T T I K L F Q E C C P H S T 154
aaaggtgctaaaattaaagaacttcgagagaacactcaaaccaccatcaagctttccaggaatgctgtcctcattccact
D R V V L I G G K P D R V V E C I K I I L D L I S E S 176
gacagagttgttcttattggaggaaaacccgatagggttgtagagtgcataaagatcatccttgatcttatatctgagtct
P I K G R A Q P Y D P N F Y D E T Y D Y G G F T M M F 198
cccatcaaaggacgtgcacagccttatgatcccaatttttacgatgaaacctatgattatggtggtttacaatgatgttt

FIG. 9

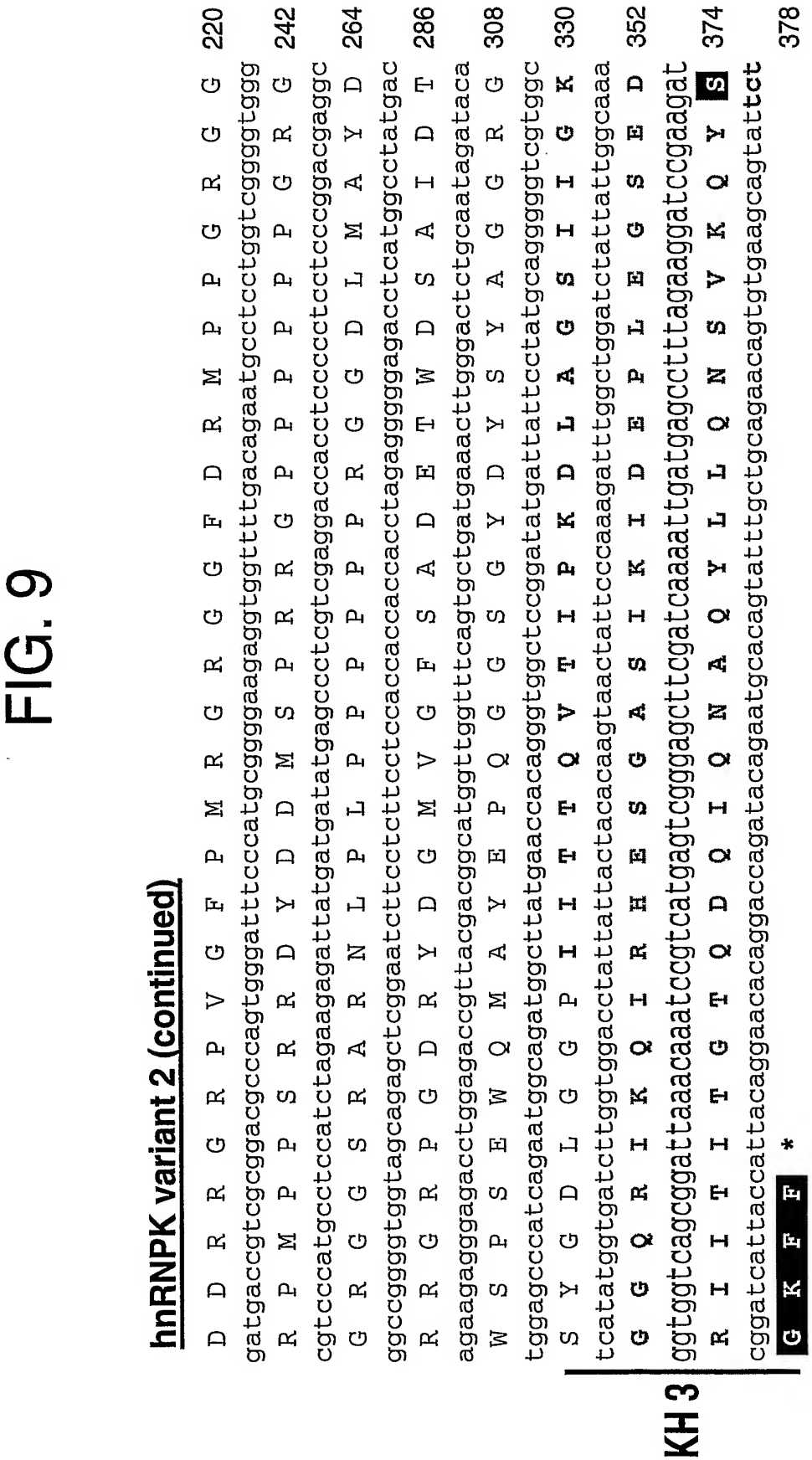

hnRNPK variant 2 (continued)
D D R R G R P V G F P M R G R G G F D R M P P G R G G 220
gatgaccgtcgcggacgcccagtgggatttcccatgcgggaagaggtggttttgacagaatgcctcctggtcgggtggg
R P M P P S R R R D Y D D M S P R R G P P P P P P G R G 242
cgtcccatgcctcctagaagagattatgatgatatgagccctcgtcgaggaccacctcccccctcctcccggacgaggc
G R G G S R A R N L P L P P P P P P R G G D L M A Y D 264
ggccgggggtggtagcagagctcggaatctttcctcctccaccaccacctagagggggagacctcatggcctatgac
R R G R P G G D R Y D D G M V G F S A D E T W D S A I D T 286
agaagagggagacctggagaccgttacgacggcatggttggtttcagtgctgatgaaacttgggactctgcaatagataca
W S P S E W Q M A Y E P Q G G S G Y D Y S Y A G G R G 308
tggagcccatcagaatggcagatggcttatgaaccacagggtggctccggatatgattattcctatgcagggggtcgtggc
S Y G D L G G P I I T T Q V T I P K D L L A G S I I G K 330
KH 3
tcatatggtgatcttggtggacctattattactacacaagtaactatttcccaaagatttggctggatctattattggcaaa
G G Q R I K Q I R H E S G A S I K I D E P L E G S E D 352
ggtggtcagcggattaaacaaatccgtcatgagtcgggagcttcgatcaaaattgatgagcctttagaaggatccgaagat
R I I T I T G T Q D Q I Q N A Q Y L L Q N S V K Q Y S 374
cggatcattaccattacaggaacacagataccagaccagtatttgctgcagaacagtgtgaagcagtattct
G K F F * 378
ggaaagttttctaa

FIG. 9

hnRNPK variant 3

```
                M  E  T  E  Q  P  E  E  T  F  P  N  T  E  T  N  G  E  F  G  K  R  P  A  E  D  M
atggaaactgaacagccagaagaaaccttccctaacactgaaaccaatggtgaatttggtaaacgccctgcagaagatatg          22
      E  E  E  Q  A  F  K  R  S  R  N  T  D  E  M  V  E  L  R  I  L  L  Q  S  K  N  A
gaagaggaacaagcatttaaaagatctagaaacactgatgagatggttgaattacgcattctgcttcagagcaagaatgct          44
      G  A  V  I  G  K  G  G  K  N  I  K  A  L  R  T  D  Y  N  A  S  V  S  V  P  D  S
KH 1  ggggcagtgattggaaaaggaggcaagaatattaaggctctccgtacagactacaatgccagtgtttcagtcccagacagc    66
      S  G  P  E  R  I  L  S  I  S  A  D  I  E  T  I  G  E  I  L  K  K  I  I  P  T  L
agtggccccgagcgcatattgagtatcagtgctgatattgaaacaattggagaaattctgaagaaaatcatccctaccttg        88
      E  E  G  L  Q  L  P  S  P  T  A  T  S  Q  L  P  L  E  S  D  A  V  E  C  L  N  Y  110
gaagagggcctgcagttgccatcacccactgcaaccagccagctcccgctcgaatctgatgctgtggaatgcttaaattac
      Q  H  Y  L  G  S  D  F  D  C  E  L  R  L  L  I  H  Q  S  L  A  G  G  I  I  G  V  132
caacactataaaggaagtgactttgactgcgagttgaggctgttgattcatcagagtctagcaggaggaattattggggtc
      K  G  A  K  I  K  E  L  R  E  N  T  Q  T  T  I  K  L  F  Q  E  C  C  P  H  S  T  154
KH 2  aaaggtgctaaaattaaagaacttcgagagaacactcaaaccaccatcaagcttttccaggaatgctgtcctcattccact
      D  R  V  V  L  I  G  G  K  P  D  R  V  V  E  C  I  K  I  I  L  D  L  I  S  E  S  176
gacagagttgttcttattggaggaaaacccgatagggttgtagagtgcataaagatcatccttgatcttatatctgagtct
      P  I  K  G  R  A  Q  P  Y  D  P  N  F  Y  D  E  T  Y  D  Y  G  G  F  T  M  M  F  198
cccatcaaaggacgtgcacagccttatgatcccaattttacgatgaaacctatgattatggtggttttacaatgatgttt
```

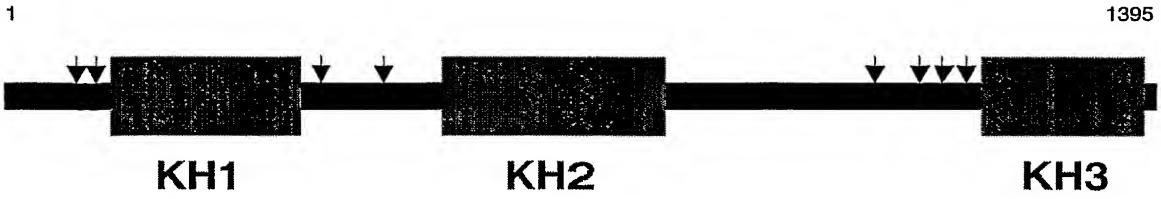
FIG. 9

hnRNPK variant 3 (continued)

```
 D  D  R  R  G  R  P  V  G  F  P  M  R  G  R  G  G  F  D  R  M  P  P  G  R  G  G  220
gatgaccgtcgcggacgcccagtgggatttcccatgcggggaagaggtggttttgacagaatgcctcctggtcggggtggg
 R  P  M  P  P  S  R  R  D  Y  D  D  M  S  P  R  R  G  P  P  P  P  P  P  G  R  G  242
cgtcccatgcctccatctagaagagattatgatgatatgagccctcgtcgaggaccacctccccctcctcccggacgaggc
 G  R  G  G  S  R  A  R  N  L  P  L  P  P  P  P  P  P  R  G  G  D  L  M  A  Y  D  264
ggccggggtggtagcagagctcggaatcttcctcttcctccaccaccaccacctagaggggagacctcatggcctatgac
 R  R  G  R  P  G  D  R  Y  D  G  M  V  G  F  S  A  D  E  T  W  D  S  A  I  D  T  286
agaagagggagacctggagaccgttacgacggcatggttggtttcagtgctgatgaaacttgggactctgcaatagataca
 W  S  P  S  E  W  Q  M  A  Y  E  P  Q  G  G  S  G  Y  D  Y  S  Y  A  G  G  R  G  308
tggagcccatcagaatggcagatggcttatgaaccacagggtggctccggatatgattattcctatgcaggggtcgtggc
 S  Y  G  D  L  G  G  P  I  I  T  T  Q  V  T  I  P  K  D  L  A  G  S  I  I  G  K  330
tcatatggtgatcttggtggacctattattactacacaagtaactattcccaaagatttggctggatctattattggcaaa
 G  G  Q  R  I  K  Q  I  R  H  E  S  G  A  S  I  K  I  D  E  P  L  E  G  S  E  D  352
ggtggtcagcggattaaacaaatccgtcatgagtcgggagcttcgatcaaaattgatgagcctttagaaggatccgaagat
 R  I  I  T  I  T  G  T  Q  D  Q  I  Q  N  A  Q  Y  L  L  Q  N  S  V  K  Q  Y  A  374
cggatcattaccattacaggaacacaggaccagatacagaatgcacagtatttgctgcagaacagtgtgaagcagtatgca
 D  V  E  G  F  *                                                                  379
gatgttgaaggattctaa
```

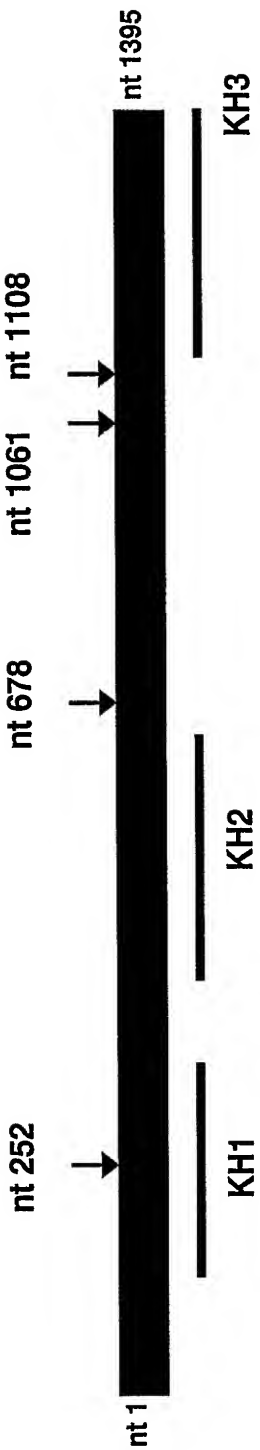
KH 3

FIG. 10



Subjects	Location	Mutation	Frequency	Variant
1	90A>G	Silent	1	V3
	112A>G	Asn > Asp	1	
	160G>A	Ala > Thr	1	
	215A>G	Tyr > Cys	1	
	1294G>A	Asp > Asn	1	
	1311T>C	Silent	1	
2	**143T>C**	Leu > Pro	1	V2
	392A>C	Asn > His	1	
3	667C>T	Missense	1	V3
4	**734A>C**	Asp > Ala	1	V3
8	**278A>T**	Asp > Val	1	V3
	469G>C	Gly > Arg	1	
	1252G>A	Gly > Arg	1	
9	252C>T	Silent	2	V3
	1242T>C	Silent	1	
10	252C>T	Silent	2	V3
	324G>T	Leu > Phe	1	
	722T>C	Met > Thr	1	
11	**664G>A**	Ala > Thr	1	V3
	1108 to 1122	Deletion	2	
	1147C>G	Pro > Gly	1	
	1174G>A	Val > Ile	1	
12	1108 to 1122	Deletion	2	V2
	1216G>T	Gly > Cys	1	
13	685T>C	Phe > Leu	1	V2
	731A>T	Asp > Val	1	
	756A>C	Silent	1	
	780T>C	Silent	1	
	1067A>T	Glu > Va	1	

FIG. 11



Location (nt)	AA change	Frequency	Source
252C>T	Silent	2 samples	this study
678C>T	Pro>Ser	not validated	dbSNP:11548847
1061A>C	Pro>Gln	not validated	dbSNP:11548850
1108 to 1122	Deletion	2 samples	this study

FIG. 12

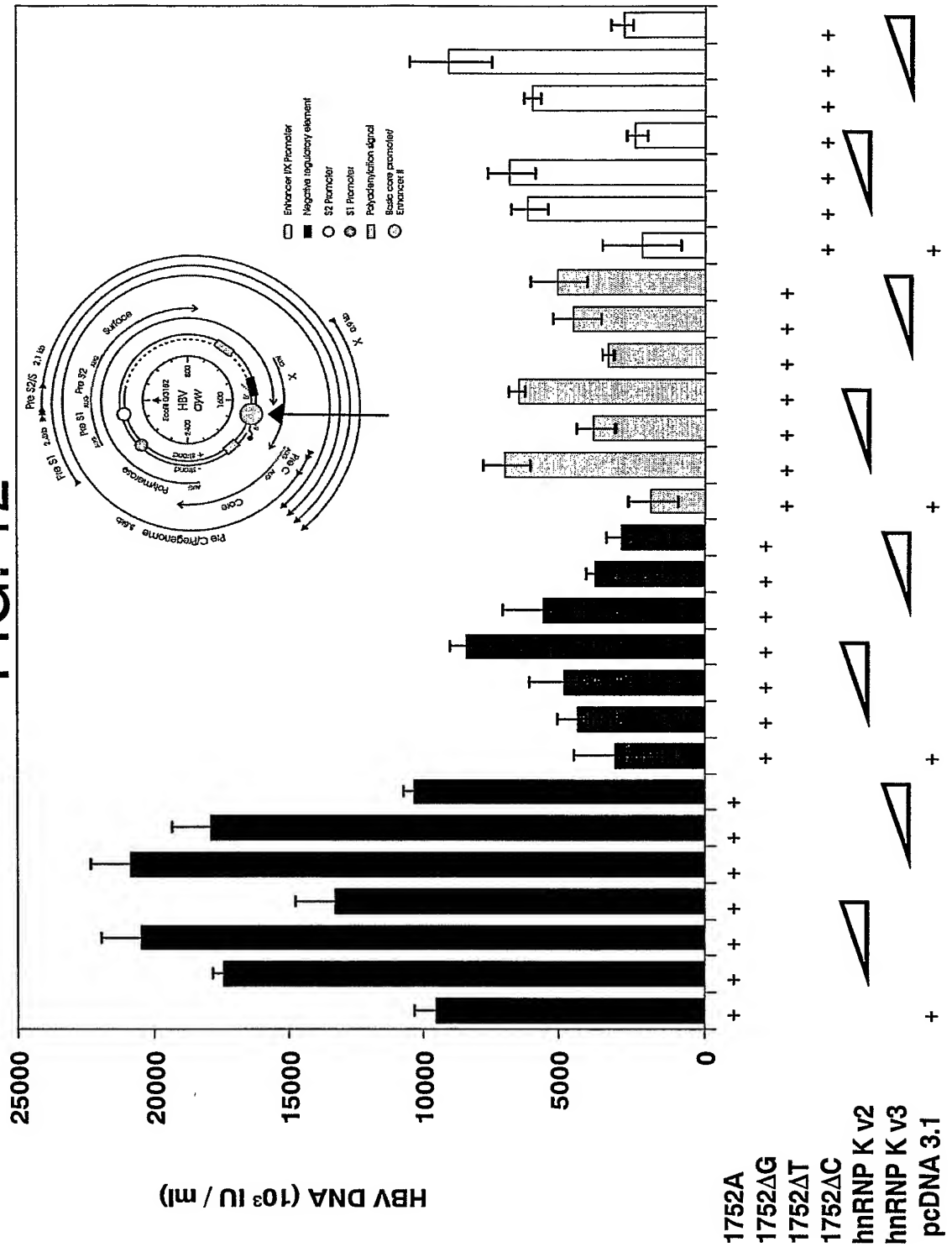

HBV DNA (10³ IU / ml)
25000
20000
15000
10000
5000
0
1752A
1752ΔG
1752ΔT
1752ΔC
hnRNP K v2
hnRNP K v3
pcDNA 3.1
Enhancer IX Promoter
Negative regulatory element
S2 Promoter
S1 Promoter
Polyadenylation signal
Basic core promoter/ Enhancer II
HBV DNA
Pre S1
Pre S2/S
Surface
Polymerase
Core
Pre C/Pregenome
X gene

FIG. 13

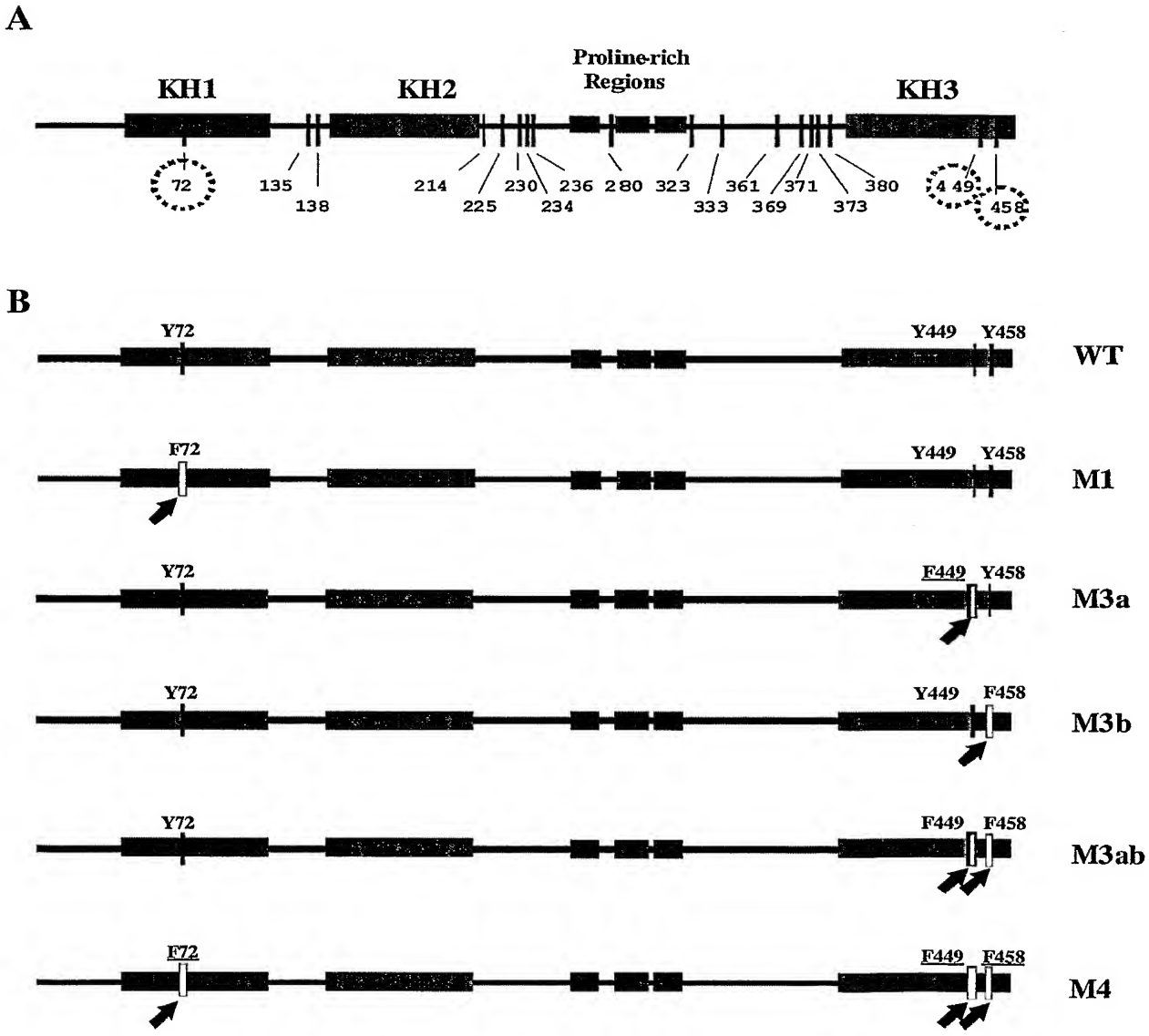

A
KH1
KH2
Proline-rich Regions
KH3
72
135
138
214
225
230
234
236
280
323
333
361
369
371
373
380
449
458
B
Y72
Y449
Y458
WT
F72
M1
F449
M3a
F458
M3b
M3ab
M4

FIG. 14

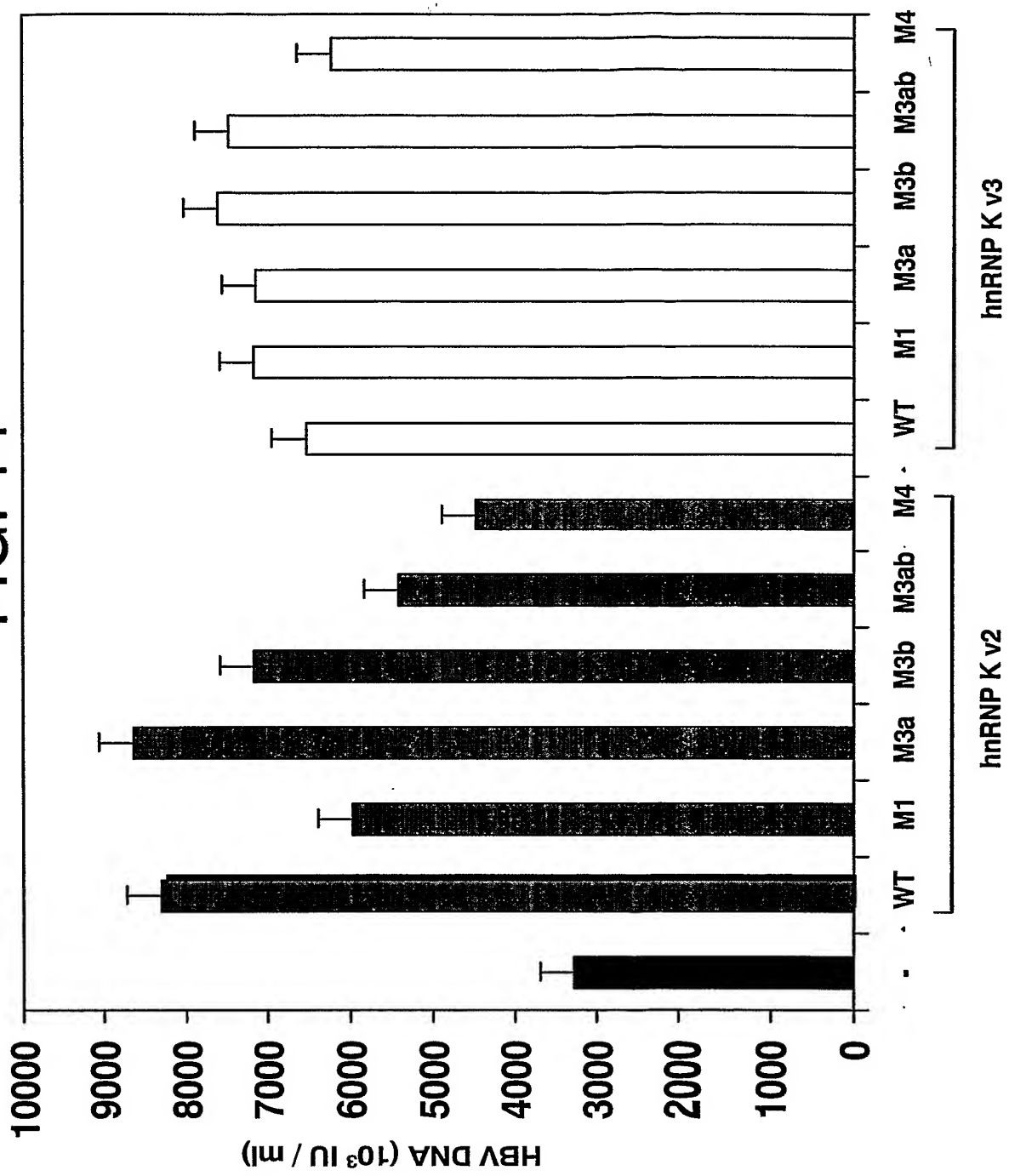

HBV DNA (10^3 IU / ml)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-
-
WT
M1
M3a
M3b
M3ab
M4
-
WT
M1
M3a
M3b
M3ab
M4
hnRNP K v2
hnRNP K v3

FIG. 15

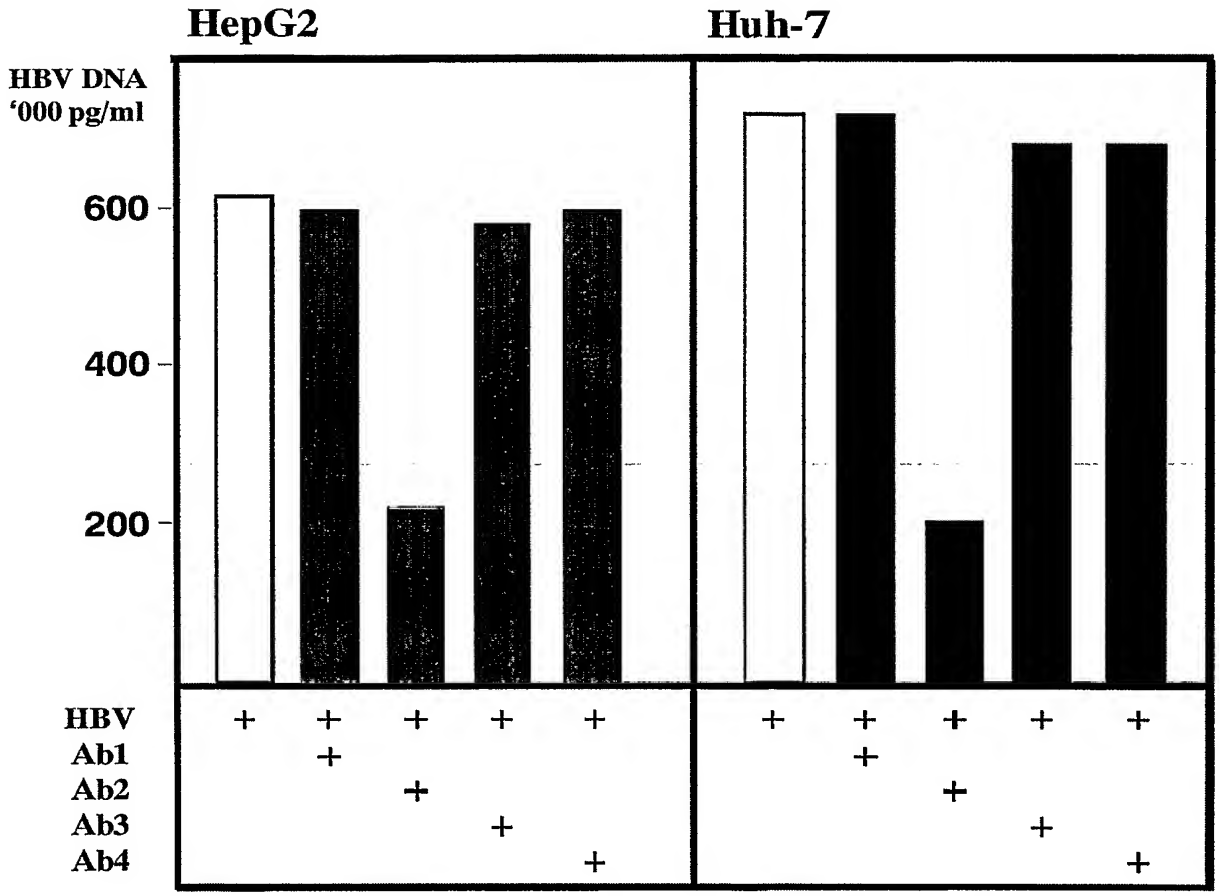


FIG. 16

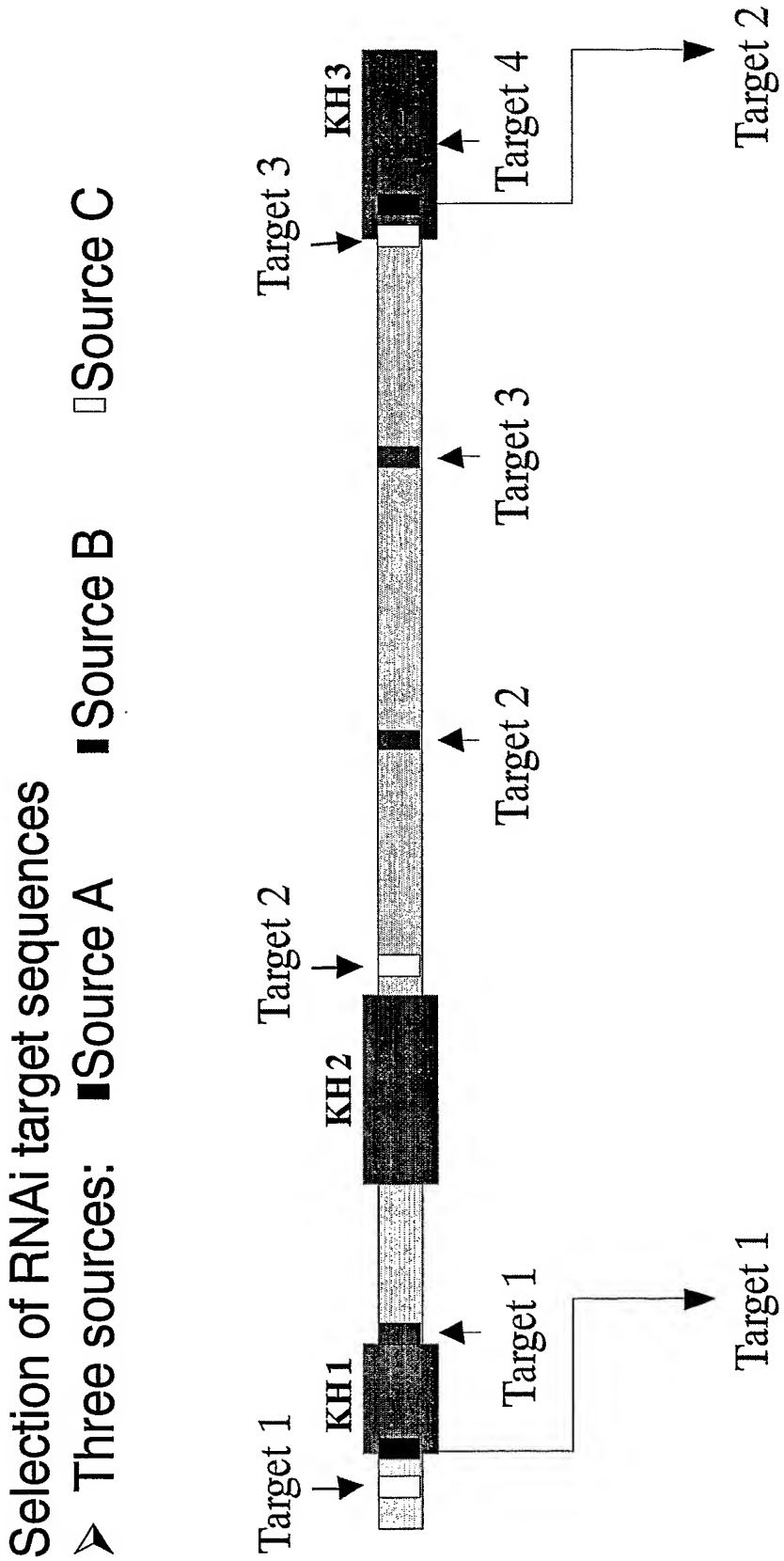

Selection of RNAi target sequences
Three sources: Source A Source B Source C
KH1
KH2
KH3
Target 1
Target 2
Target 3
Target 4
Target 1
Target 2
Target 3
Target 1
Target 2

FIG. 17

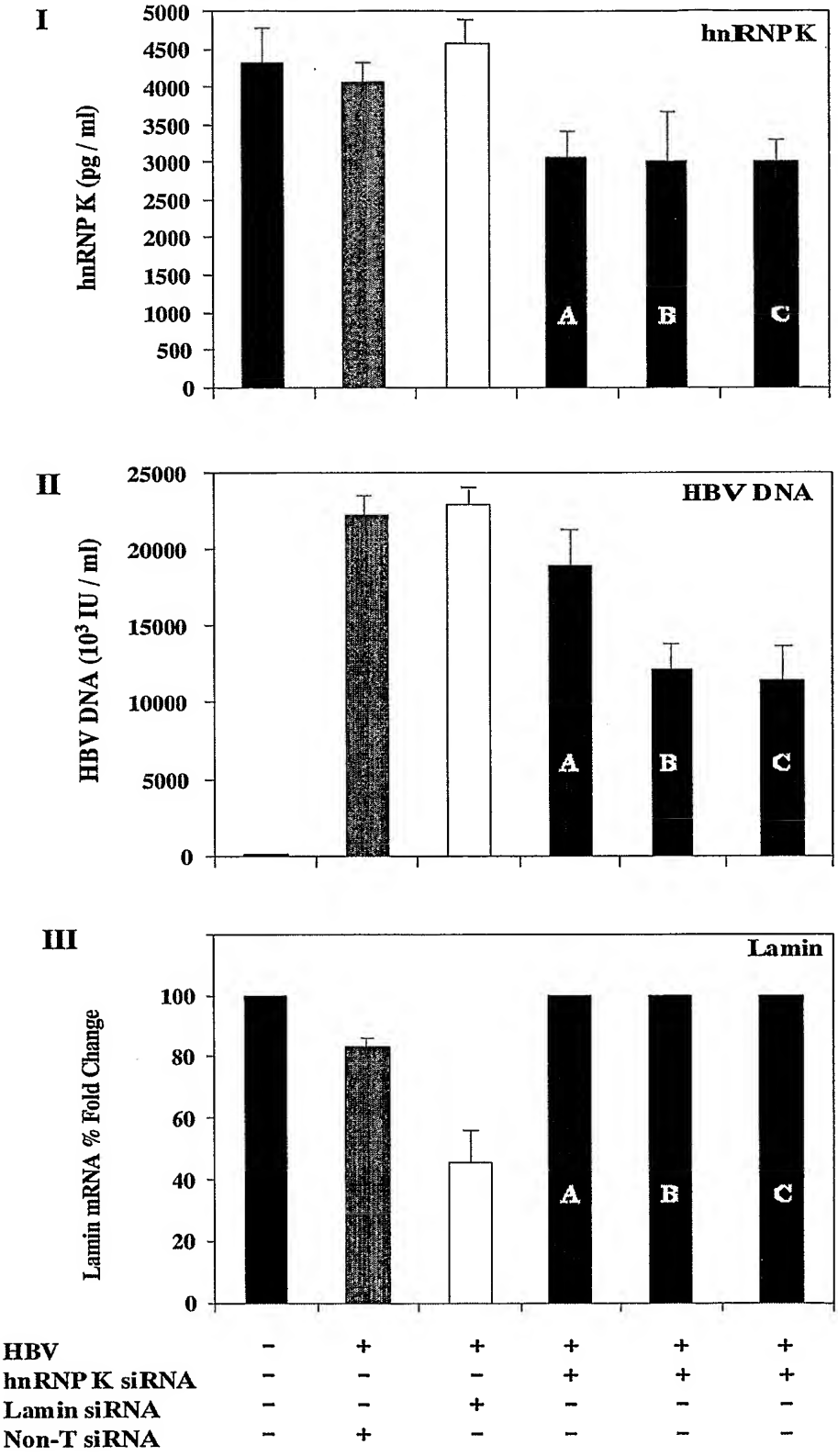

I
hnRNP K
hnRNP K (pg / ml)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
A
B
C
II
HBV DNA
HBV DNA (10³ IU / ml)
25000
20000
15000
10000
5000
0
A
B
C
III
Lamin
Lamin mRNA % Fold Change
100
80
60
40
20
0
A
B
C
HBV - + + + + +
hnRNP K siRNA - - - + + +
Lamin siRNA - - + - - -
Non-T siRNA - + - - - -

FIG. 18

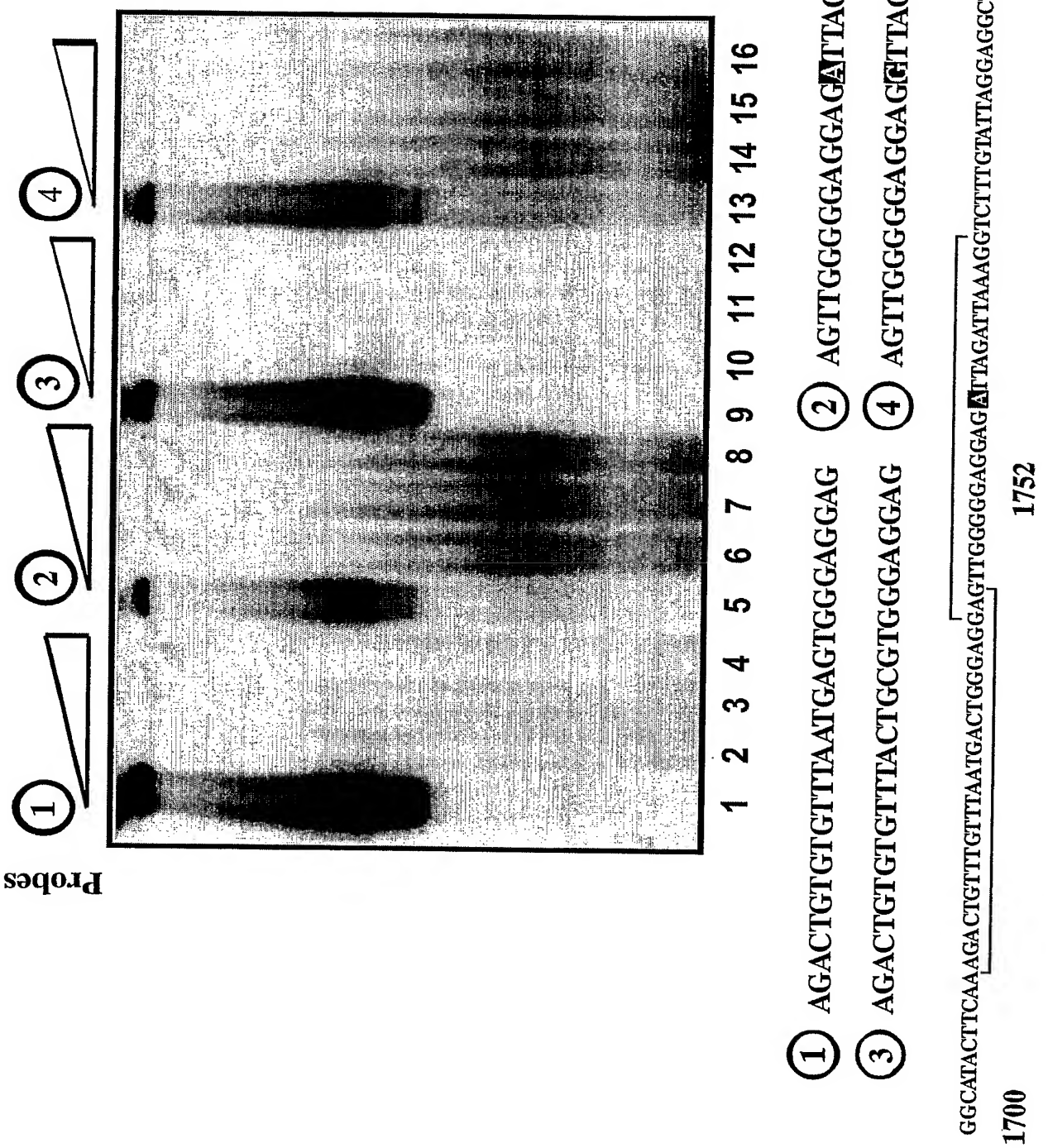

Probes
1
2
3
4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
1 AGACTGTGTGTTTAATGAGTGGGAGGAG
3 AGACTGTGTGTTTACTGCGTGGGAGGAG
2 AGTTGGGGGAGGAGATTAGGTTAAAGGT
4 AGTTGGGGGAGGAGCTTAGGTTAAAGGT
1700
GGCATACTTCAAAGACTGTTTGTTTAATGACTGGGAGGAGTTGGGGGAGGAGATTAGATTAAAGGTCTTTGTATTAGGAGGCTGTAGGCATAAATTGGTCT
1752
1800

FIG. 19

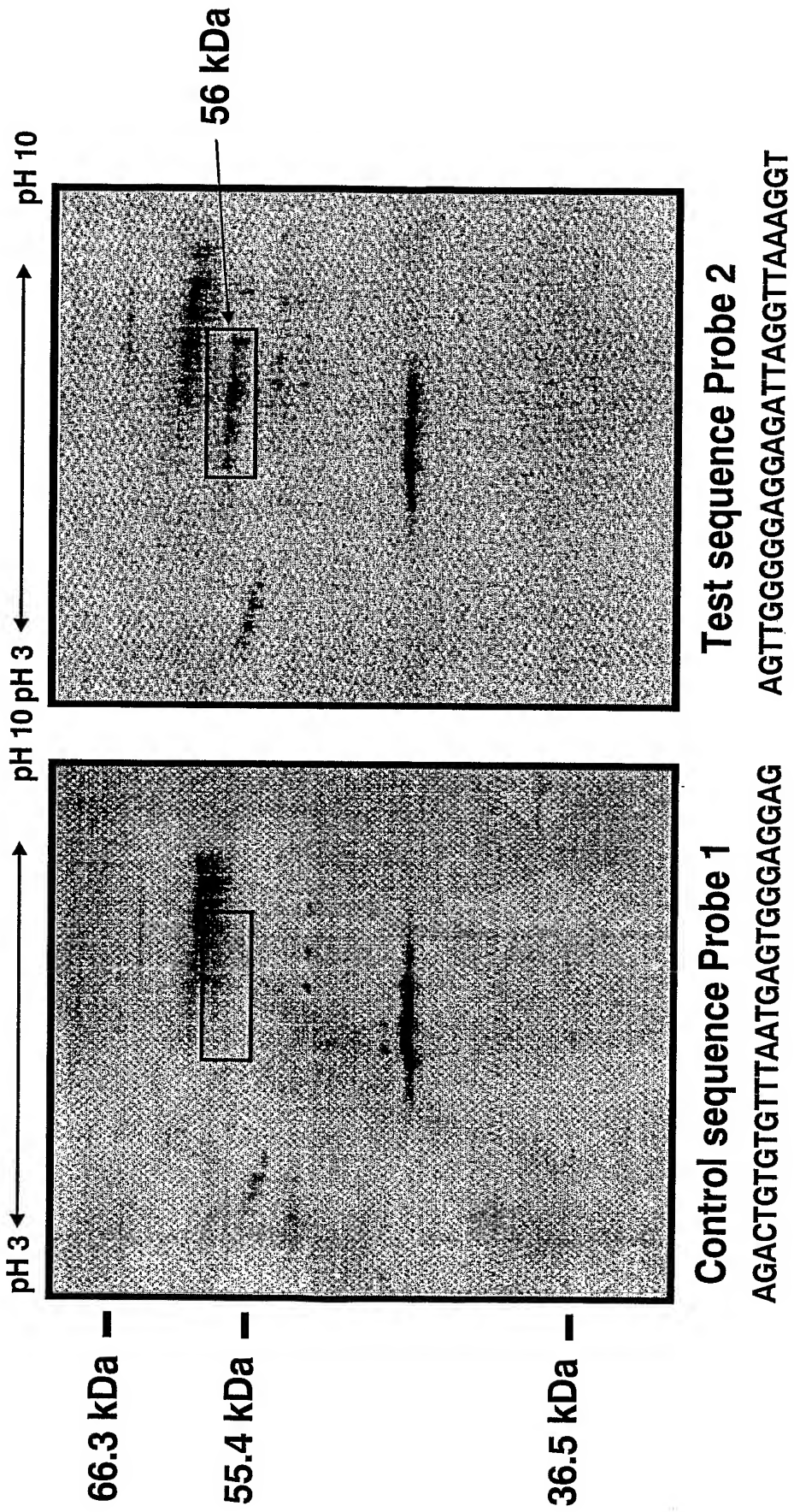

56 kDa
pH 10
pH 10 pH 3
pH 3
Test sequence Probe 2
AGTTGGGGGAGGAGATTAGGTTAAAGGT
Control sequence Probe 1
AGACTGTGTGTTTAATGAGTGGGAGGAG
66.3 kDa
55.4 kDa
36.5 kDa

FIG. 20

Mass: 48708 **Total score:** 607 **Peptides matched:** 21

Query	Observed	Mr(expt)	Mr(Calc)	Score	Peptide
3	437.2488	872.4821	872.4967	16	DLAGSIIGK
5	499.2279	996.4402	996.4334	44	GGDLMAYDR
8	351.8774	1052.6088	1052.6088	33	VVLIGGKPDR
9	549.7244	1097.4332	1097.4573	27	GSDFDCELR
10	553.7588	1105.5019	1105.5073	55	NTDEMVELR
11	385.1795	1152.5150	1152.5345	39	GGDLMAYDRR
12	390.5085	1168.5021	168.5294	(19)	GGDLMAYDRR
13	597.8453	1193.6749	1193.6920	29	NLPLPPPPPPR
14	597.8495	1193.6833	1193.6920	(18)	NLPLPPPPPPR
15	597.8527	1193.6898	1193.6920	(24)	NLPLPPPPPPR
16	630.2869	1258.5582	1258.5677	60	IDEPLEGSEDR
17	670.8989	1339.7822	1339.7962	88	IILDLISESPIK
18	450.5459	1348.6142	1348.6405	45	SRNTDEMVELR
21	506.9706	1517.8884	1517.9293	18	LLIHQSLAGGIIGVK
22	511.9268	1532.7569	1532.7874	22	IIPTLEEYQHYK
24	517.2101	1548.6068	1548.6701	16	LFQECCPHSTDR
25	518.6332	1552.8761	1552.9188	16	IILDLISESPIKGR
27	579.2644	1734.7697	1734.7995	15	RPAEDMEEEQAFKR
28	594.2626	1779.7642	1779.7911	(12)	TDYNASVSVPDSSGPER
29	890.9033	1779.7910	1779.7911	62	TDYNASVSVPDSSGPER
33	707.6703	2119.9874	2120.0134	23	ALRTDYNASVSVPDSSG

FIG. 21

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hnRNPK variant 2    METEQPEETFPNTETNGEFGK RPAEDMEEEQAFKRSRNTDEMVELR ILLQSKNAGAVIGKGGKNIK ALRTDYNASVSVPD80
hnRNPK variant 3    METEQPEETFPNTETNGEFGK RPAEDMEEEQAFKRSRNTDEMVELR ILLQSKNAGAVIGKGGKNIK ALRTDYNASVSVPD80
HBV-binding protein ---------------------- RPAEDMEEEQAFKRSRNTDEMVELR ---------------------- ALRTDYNASVSVPD

hnRNPK variant 2    SSG PERILSISADIETIGEILKKIIPTLEEGLQLPSPTATSQLPLESDAVECLNYQHYK GSDFDCELRLLIHQSLAGGII160
hnRNPK variant 3    SSG PERILSISADIETIGEILKKIIPTLEEGLQLPSPTATSQLPLESDAVECLNYQHYK GSDFDCELRLLIHQSLAGGII160
HBV-binding protein SSG ---------------------------------------------------------- GSDFDCELRLLIHQSLAGGII

hnRNPK variant 2    GVK GAKIKELRENTQTTIK LFQECCPHSTDRVVLIGGKPDR VVECIK IILDLISESPIKGR AQPYDPNFYDETYDYGGFT240
hnRNPK variant 3    GVK GAKIKELRENTQTTIK LFQECCPHSTDRVVLIGGKPDR VVECIK IILDLISESPIKGR AQPYDPNFYDETYDYGGFT240
HBV-binding protein GVK ---------------- LFQECCPHSTDRVVLIGGKPDR ------ IILDLISESPIKGR ----------------------

hnRNPK variant 2    MMFDDRRGRPVGFPMRGRGGFDRMPPGRGGRPMPPSRRDDYDDMSPRRGPPPPPPGRGGSRAR NLPLPPPPPPRGGDLMA320
hnRNPK variant 3    MMFDDRRGRPVGFPMRGRGGFDRMPPGRGGRPMPPSRRDDYDDMSPRRGPPPPPPGRGGSRAR NLPLPPPPPPRGGDLMA320
HBV-binding protein ------------------------------------------------------------ NLPLPPPPPPRGGDLMA

hnRNPK variant 2    YDRR GRPGDRYDGMVGFSADETWDSAIDTWSPSEWQMAYEPQGGSGYDYSYAGGRGSYGDLGGPIITTQVTIPKDLAGSI400
hnRNPK variant 3    YDRR GRPGDRYDGMVGFSADETWDSAIDTWSPSEWQMAYEPQGGSGYDYSYAGGRGSYGDLGGPIITTQVTIPKDLAGSI400
HBV-binding protein YDRR ------------------------------------------------------------------------------

hnRNPK variant 2    IGKGGQRIKQIRHEGASIK IDEPLEGSEDR IITITGTQDQIQNAQYLLQNSVKQYSGKFF460
hnRNPK variant 3    IGKGGQRIKQIRHEGASIK IDEPLEGSEDR IITITGTQDQIQNAQYLLQNSVKQYADVEGF461
HBV-binding protein ------------------- IDEPLEGSEDR ----------------------------
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